

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE**

A. 510(k) Number:

k121944

B. Purpose for Submission:

New device

C. Measurand:

Renin

D. Type of Test:

Quantitative

E. Applicant:

DiaSorin Inc.

F. Proprietary and Established Names:

LIAISON® Direct Renin,
LIAISON® Control Direct Renin,
LIAISON® Endocrinology Diluent

G. Regulatory Information:

1. Regulation section:
21 CFR § 862.1085, 21 CFR § 862.1660
2. Classification: Class II, Class I, reserved
3. Product code:
CIB, Angiotensin I and renin test system
JJX, Quality control
4. Panel:
Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):
See indications for use below.
2. Indication(s) for use:
The LIAISON® Direct Renin assay uses chemiluminescent immunoassay (CLIA) technology on the LIAISON® Analyzer and is intended for the quantitative determination of renin in human EDTA plasma. Renin measurements may aid in the diagnosis and treatment of certain types of hypertension.

The DiaSorin LIAISON® Control Direct Renin is used in conjunction with the

LIAISON® Direct Renin assay for quality control of Renin assay.

The DiaSorin LIAISON® Endocrinology Diluent is intended for use with the LIAISON® Direct Renin assay for the dilution of samples which read above the upper limit of the assay measurement range (300 pg/mL).

3. Special conditions for use statement(s):
Prescription use only
4. Special instrument requirements:
Liaison analyzer

I. Device Description:

LIAISON® Direct Renin is an in vitro diagnostic device consisting of reagents provided in individual compartments within a plastic container called the Reagent Integral and reagents supplied ready to use in vials. The Reagent Integral includes: magnetic particles (2.3 ml) and conjugate (13 ml). The assay configuration allows performance of 100 tests. The components, provided in the unitized Reagent Integral include: PMP (paramagnetic particles) and conjugate. The two calibrators A and B are provided in the same box, but separate from the Reagent Integral. The calibrators are made from recombinant human renin, phosphate buffer, BSA, an inert yellow dye, preservatives and antibiotics. The calibrators are lyophilized and must be reconstituted using distilled water prior to use. LIAISON® Control Direct Renin kit consisting of two levels of control materials are made from recombinant human rennin phosphate buffer, BSA, preservatives and antibiotics. Control level 1 is intended to provide an assay response characteristic of low level patient specimens (target value: 15 pg/mL). Control level 2 is intended to provide an assay response characteristic of high level patient specimens (target value: 55 pg/mL).

J. Substantial Equivalence Information:

1. Predicate device name(s):
Renin III Generation (CIS BIO INTERNATIONAL)
LIAISON® 25 OH Vitamin D TOTAL Control (DIASORIN, INC.)
2. Predicate 510(k) number(s):
k062120 (assay)
k071480 (control)
3. Comparison with predicate:

a. Renin assay

Similarities		
Item	Candidate Device	Predicate (k062120)
Intended Use	Quantitative determination of active renin in human EDTA plasma	Same
Type of Assay	Sandwich Assay Sandwich	Same
Sample Matrix	EDTA plasma	Same
Calibrated to a WHO Standard	First World Health Organization International Reference Preparation (68/356)	Same
Unit of Measure	pg/mL	Same
Capture Mouse Reagent	Mouse monoclonal anti- renin	Same

Differences		
Item	Device	Predicate
Sample handling/processing	Automated	Manual
Detector	Mouse monoclonal anti-renin conjugated to isoluminol derivative	Radio-labeled anti-human renin
Calibration	Two-point verification of stored 10-point master curve.	Perform with each assay
Reagent Storage	On-board or in refrigerator	Refrigerator only.
Measuring Range	2.1 - 300 pg/mL	1.0 - 320 pg/mL
Measurement System	Photomultiplier (flash chemiluminescence reader)	Gamma counter
Total Incubation Time	30 minutes	180 minutes
Sample Size	200 uL	300 uL

b. Renin control

Item	LIAISON® Control Direct Renin	LIAISON® 25 OH Vitamin D TOTAL Control (K071480)
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Intended Use	The DiaSorin LIAISON® Control Direct Renin is used in conjunction with the LIAISON® Direct Renin assay for quality control of the Renin assay.	The LIAISON® 25 OH Vitamin D TOTAL Control Set is intended for use as assayed quality control samples to monitor the accuracy and precision of the LIAISON® 25 OH Vitamin D TOTAL Assay.
Storage	Store at 2-8°C until ready to use	Same
Matrix	Lyophilized recombinant human renin, phosphate buffer, BSA, Preservatives: ProClin® 300 and Gentamicin Sulfate	Liquid human serum-based controls provided in vials with buffer salts and sodium azide.
Levels	2 levels: low and high	Same

K. Standard/Guidance Document Referenced (if applicable):

None identified

L. Test Principle:

The method for the quantitative determination of renin is a sandwich chemiluminescence immunoassay that uses two anti-renin monoclonal antibodies. One specific mouse monoclonal antibody is coated on the magnetic particles (solid phase), that recognizes both renin and prorenin; another monoclonal antibody (specific for renin) is linked to an isoluminol derivative (isoluminolantibody conjugate). During the incubation, renin bound to the solid phase and a sandwich is formed only in the presence of renin molecules that bridge both antibodies. The unbound material is removed with a wash cycle during post-incubation period. Finally a flash chemiluminescence reaction is thus induced by a starter reagent and the light signal is measured by a photomultiplier as relative light units (RLU) using LIAISON® Analyzer.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

A twenty day reproducibility/precision study was performed to demonstrate the precision of the assay using six (6) EDTA plasma samples and two controls that were measured multiple times at three different locations. These studies were tested on two lots of LIAISON® Direct Renin - 2 lots at each site in two replicates per run, 2 runs per day for 20 operating days. The overall results are as follows:

Panel ID#	N	mean pg/mL	within run SD	within run %CV	Total/Across Lots/Across Sites SD	Total/Across Lots/Across Sites %CV
Level 1	480	14.4	0.94	6.6%	1.44	10.0%
Level 2	480	55.3	0.75	1.4%	2.49	4.5%
POOL1	480	12.8	0.42	3.3%	1.22	9.5%
POOL2	480	31.7	0.87	2.7%	1.81	5.7%
POOL3	480	53.0	1.17	2.2%	2.50	4.7%
POOL4	480	78.8	0.91	1.2%	3.21	4.1%
POOL5	480	110.0	2.79	2.5%	5.66	5.1%
POOL6	480	166.0	2.32	1.4%	9.90	6.0%

b. Linearity/assay reportable range:

A total of 12 serial diluted concentrations were tested in replicates of four ranging between 2.0 to 309.1 pg/ml to examine the linearity of the study.

A linear regression result is showed as $Y \text{ (Obtained)} = 1.008X \text{ (Expected)} + 0.27$, $R=0.998$ between expected and observed concentration for all dilutions of each pool.

The data provided support the sponsor's claim that the measuring range of this assay is 2.1 to 300 ng/mL.

c. Traceability:

The assigned renin values of the assays are traceable to the WHO reference materials (68/356).

Stability Studies:

The stability of the calibrator and control are based on real-time stability study data. The stability study protocol and acceptance criteria were provided and found to be acceptable. The shelf-life of calibrator and control are stable until expiration date (18 months) at 2-8°C.

Open vial stability:

After reconstitution, calibrator is stable for 2 weeks at 2-8°C and control is stable for 8 weeks at 2-8°C.

Value Assignment of Calibrators and Controls

The initial lot of calibrator materials is value assigned through an internal procedure. The value ranges of calibrator A and B are 5-10 pg/ml and 85-125 pg/ml respectively. The calibrators will be tested using the assay and they must fall within above target ranges. Otherwise, the calibrators will be adjusted by dilution.

The value of control materials was assigned through an internal procedure. The procedure includes 1) Check of the bulk preparation 2) Check after lyophilization and value assignment using approved Reagent Integral lots to assign the target value 3) Check after labeling and packaging.

The target values of Control level 1 and 2 are 15 pg/mL and 55 pg/mL, respectively.

d. Detection limit:

The Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ) were calculated based on CLSI EP17-A.

Five aliquots of calibrator matrix (without renin) were tested in triplicates in four runs with two different kit lots on two different instruments (60 determinations per lot), and used to calculate the Limit of Blank (LoB) on each kit lot, as 95th percentile. The overall assay's LoB is the higher of the two kit lot LoBs.

$LoB = \text{Mean} + 1.671 * SD$ where SD is the mean standard deviation. The LoB was calculated to be 0.1.

Then four samples at low renin level were tested in triplicates in four runs with two different kit lots and instruments. The results of two lots were used to calculate the Limit of Detection (LoD) (48 determinations per lot) of each assay lot. The overall assay's LoD is the higher of the two kit lot LoDs.

$LoD = LoB + 1.68 * SD$ where SD is the mean standard deviation. The LoD was calculated to be 1.03.

The Limit of Quantitation (LoQ) was determined as the mean concentration at which the mean %CV exceeded 20%. It was calculated by testing six specimens at low renin doses and assayed in 72 determinations on two different kit lots and two different instruments. The mean, standard deviation, and %CV was then determined for each sample. The LoQ was calculated to be 2.1.

The data provided support the sponsor's claim that the measuring range of this assay is 2.1 to 300 ng/mL.

e. *Analytical specificity:*

An interference study was evaluated according to CLSI EP17-A2 guideline. No significant interference was observed when samples were spiked with the following potential interference substances. These testings were based on CLSI-EP07-A2 guideline. Non-significant interference was defined as difference from control (unspiked sample) within $\pm 10\%$. Results of the interference study are summarized in the table below.

Substance	Tested Concentration	Substance	Tested Concentration
Triglycerides	3000 mg/dl	Captopril	5 $\mu\text{g/mL}$
Hemoglobin	1000 mg/dL	Captopril disulphide	1.6 $\mu\text{g/mL}$
Unconjugated bilirubin	20 mg/dL	Enalapril dehydrate (Renitec)	0.4 $\mu\text{g/mL}$
Conjugated bilirubin	30mg/dL	Nicardipine (Loxen)	50 $\mu\text{g/mL}$
Albumin	6000 mg/dL	Furosemide (Lasilix)	60 $\mu\text{g/mL}$
Prorenin	10 ng/mL	Vitamin H	200 ng/mL
Cathepsin D	0.5 U/mL	HAMA	1500 ng/mL
Cathepsin B	0.1 U/mL		

A hook effect study was performed using 3 high renin concentration samples, out-of-range (up to 609.7 pg/mL). Samples were serially diluted in renin-stripped plasma and Liaison® Endocrinology Diluent. The neat sample and the dilutions were tested in triplicates using one kit lot on one Analyzer. For each sample the signal obtained were plotted versus the concentration and no hook effect were observed with Renin concentration up to 609.7 pg/mL.

f. *Assay cut-off:*

Not applicable.

2. Comparison studies:

a. *Method comparison with predicate device:*

A study was performed to compare the results of the LIAISON® Direct Renin test to CisBio Renin Assay (Predicate) using 173 renin samples based on CLSI EP9-A guidelines. The range of results observed with the DiaSorin LIAISON® Direct Renin test ranged 2.4 to 285 pg/ml. Passing Bablok regression analysis and difference plots were applied to these samples, yielding the following regression: $Y = 1.02 X - 0.11$, $r^2 = 0.9732$. The 95% confidence interval for the slope was 0.99 to 1.07, and the 95% confidence interval for the intercept was -0.70 to 0.59 pg/mL.

- b. *Matrix comparison:*
Not applicable.
3. Clinical studies:
- a. *Clinical Sensitivity:*
Not applicable.
- b. *Clinical specificity:*
Not applicable.
- c. *Other clinical supportive data (when a. and b. are not applicable):*
Not applicable.
4. Clinical cut-off:
Not applicable.
5. Expected values/Reference range:

In order to determine the normal range of LIAISON® Direct Renin assay, 266 EDTA samples from 133 subjects, apparently healthy subjects' ages 18 to 65 years were analyzed using the LIAISON® Direct Renin kit. Blood was collected between 7:00 a.m. and 10:00 a.m. with the subjects either in an upright or supine position. Upright samples were collected with individuals sat down to have their blood withdrawn and tested using the LIAISON® Direct Renin kit after standing for 30 minutes; supine samples were collected after the individuals lay in supine position for at least 30 minutes. The results are shown in the Table below.

Results	Age	N	Mean (pg/mL)	S.D.	Range
Upright	≤40	81	18.2	12.4	4.2-52.2
	>40	52	15.6	11.8	3.6-81.6
Supine	≤40	81	12.5	8.8	3.2-33.2
	> 40	52	10.5	6.8	3.1-45.1

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.